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Orodispersible tablets containing taste-masked solid lipid pellets with metformin hydrochloride: Influence of process parameters on tablet properties

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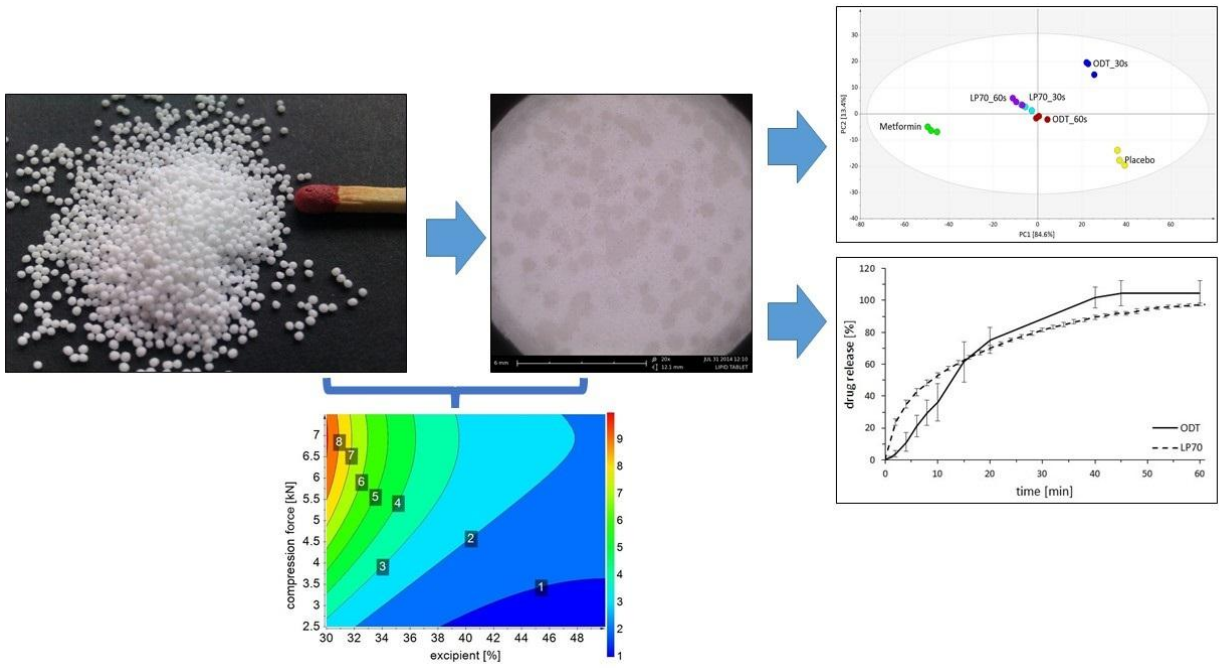
Graphical abstract



Abstract

Compaction of multiparticulates into tablets, particularly into orodispersible tablets (ODTs), is challenging. The compression of pellets, made by solid lipid extrusion/spheronization processes, presents peculiar difficulties since solid lipids usually soften or melt at relatively low temperature ranges and due to applied mechanical forces. Until now, there are no reports in literature about the development of ODTs based on solid lipid pellets. To investigate the feasibility of producing such tablets, a design of experiment (DoE) approach was performed to elucidate the influence of compression force and amount of two co-processed excipients (Ludiflash® and Parteck® ODT) on properties of the tablets (friability, tensile strength, and disintegration time). ODTs (15 mm, flat-faced) with solid lipid pellets (250-1000 µm in diameter) containing 500 mg of metformin HCl, presenting immediate drug release profile and taste-masked properties, were targeted. During compression, a strong lamination of the tablets containing Parteck® ODT was observed. This phenomenon was prominently observed when high compression forces (≥ 5 kN) and high excipient amounts (≥ 40%; w/w) were used. On the other hand, the DoE focused on tablets with Ludiflash® showed

better results regarding the production of ODTs. A positive influence of the compression force on the tensile strength, friability, and disintegration time of the tablets, regarding specifications of the Ph. Eur., was observed. The increase in the amount of this excipient resulted in fast disintegrating tablets, however, a negative influence on the tensile strength was noticed. After optimization of the parameters and formulation, based on the DoE results and considering the Ph. Eur. specifications for tablets, ODTs based on lipid pellets containing metformin HCl presenting immediate release profile (85% drug release in less than 30 min) and taste-masked properties (determined by an electronic tongue) were successfully obtained.

KEYWORDS: Orodispersible tablets, lipid pellets, metformin hydrochloride, compression force, taste-masking, DoE

1. Introduction

Recently, orodispersible tablets (ODTs) are becoming popular solid oral dosage forms, in particular for pediatric and geriatric use [1]. Compaction of multiparticulates into tablets, particularly into ODTs, is a challenging area. In particular, the compression of pellets based on solid lipid excipients presents peculiar difficulties to be overcome, since they usually soften or melt at low temperature ranges [2]. These thermal properties could negatively influence the compaction process and furthermore the tablet properties [3]. There are several methodologies regarding the production of solid lipid pellets reported in the literature, however, solvent-free cold extrusion followed by spheronization is most recently receiving an increasing attention due to its advantages in producing immediate release pellets presenting taste-masked properties [4-6]. Regarding the compaction of such pellets, formulation scientist must have a comprehensive knowledge of how the pellets will behave during tableting, as well as how the material and/or process-related parameters will affect the performance of the formulation as a drug delivery system [7].

There are several ready-to-use excipients in the market to produce ODTs, which are designed to improve the disintegration process of the solid dosage form. Most of them are co-processed mixtures based on mannitol, such as Ludiflash® and Parteck® ODT. Mannitol is a low-digestible sugar alcohol that presents supplementary benefits as pharmaceutical excipients for oral solid dosage forms: its reduced caloric content compared to other sugar derivates excipients, its low glycemic response, and its non-cariogenic properties [8]. Mannitol has been used as a filler in chewable tablets due to its pleasant taste and convenient mouth-feel for oral dosage forms. Additionally, its exhibits a negative heat of solution and imparts a cooling sensation when sucked or chewed [9].

Regarding the compaction of multiple unit systems, such as pellets, ready-to-use excipient can be used to fill the void space between the pellets to be compressed and act as cushioning agent to absorb the compression force [10]. At the same time, filler materials can be employed to disperse individual pellets, preventing direct contact, by forming a layer around the pellets. This function should be investigated to avoid adhesion or

formation of solid bridges between the lipids that are contained in the pellet formulation. The establishment of such bridges could lead to the formation of a water insoluble matrix, which could negatively influence the disintegration process of the ODTs and furthermore their drug release profile.

In the present work, metformin hydrochloride was chosen as model drug. Metformin HCl is a biguanide used in the treatment of type 2 diabetes *mellitus*. Oral tablets containing metformin HCl presenting immediate release profile and doses of 500 mg until 1 g are generally encountered in the market. Treatments with traditional oral tablets, containing these high doses, are commonly discontinued due to patient's difficulty in swallowing those dosage forms [11, 12]. Generally, the tablets are crushed (and mixture with food or beverages) or splinted to overcome swallowing issues. However, metformin HCl presents a strong bitter taste, and these procedures increase bitter taste recognition and could lead to patient rejection [13-15].

There are no reports in literature about investigations or the development of ODTs based on solid lipid pellets produced by cold extrusion/spheronization. This work aims to evaluate the feasibility of producing ODTs containing 500 mg of metformin HCl, presenting immediate-release profile and taste-masked properties. Besides, this work focuses on the investigation of the influence of the use of different ready-to-use excipients and the investigation if the effect of compression force on the tablet properties.

2. Material and Methods

2.1. Materials

Metformin hydrochloride (Wanbury, Maharashtra, India), a powdered hard fat (Witocan® 42/44 mikrofein, Cremer Oleo, Witten, Germany), glyceryl distearate (Precirol® ATO 5, Gattefossé, Weil am Rhein, Germany), and glyceryl trimyristate (Dynasan® 114, Cremer Oleo, Witten, Germany) were sieved through a 300 µm sieve prior to usage. The mannitol containing ready-to-use excipients Ludiflash® (BASF SE, Ludwigshafen, Germany) and Parteck® ODT (Merck KGaA, Darmstadt, Germany) were used as received.

2.2. Preparation of the Pellets

Metformin HCl was blended with hard fat, glyceryl distearate, and glyceryl trimyristate at a ratio of 19:6:1:1, respectively, for 15 min at 25 rpm (LM40, Bohle, Ennigerloh, Germany) to produce a batch of 300 g of pellets. The extrusion was performed on a co-rotating twin-screw extruder (Mikro 27GL-28D, Leistritz, Nuremberg, Germany). Batches of 300 g of extrudates were rounded for 15 min at 1500 rpm using in a spheronizer (RM 300, Schlüter, Neustadt, Germany). The parameters were adjusted aiming to heat the material up to 33 °C according to our prior work [16]. The produced pellets were sieved and the fraction between 250 and 1000 µm was further used.

2.3. Design of Experiments (DoE)

The influence of the compression force (Com) and amount of commonly used co-processed excipients (Exc) (Ludiflash® and Parteck® ODT) on the tablet disintegration time, friability, and tensile strength was

investigated. The conception and statistical evaluation of the experimental project to the development of the ODTs was performed using Software Modde v. 9.0 (Umetrics, Umea, Sweden). A factorial design based on 2 quantitative factors (Com and Exc) at three levels each (3^2 design) was performed for the two ready-to-use excipients (Table 1). Three repetitions were made at the center point of the DoE to estimate the repetition error ($\mathcal{E}$), resulting in 22 experiments. The quality of the design is described by the goodness of fit (R^2), goodness of prediction (Q^2), reproducibility, and validity. The complete used model equation contains 2 linear factors, 2 quadratics, and one interaction term as shown in the following equation:

$$y = \beta_0 + \beta_{Exc}x_{Exc} + \beta_{Com}x_{Com} + \beta_{Exc\cdot Exc}x_{Exc}^2 + \beta_{Com\cdot Com}x_{Com}^2 + \beta_{Exc\cdot Com}x_{Exc}x_{Com} + \mathcal{E} \quad \text{(Equation 1)}$$

where "Exc" is the amount of excipient and "Com" is the used compaction force.

2.3.1. Preparation of the Tablets

Tablets were produced in an instrumented single-punch press machine (EK0, Korsch, Berlin, Germany) employing 15 mm flat-faced punches. The amount of pellets was adjusted aiming tablets containing 500 mg of metformin HCl (Table 2). Excipient and lipid pellets were blended in a laboratory mixer (LM20, Bohle, Ennigerloh, Germany) for 15 min at 25 rpm. Batches of 100 tablets for each excipient were produced.

2.3.2. Tensile Strength of Tablets

The tensile strength of 20 tablets was determined individually, measuring the radial crushing force (F) in a tablet crushing strength apparatus (HT1, Sotax, Aesch, Switzerland). The dimensions (thickness h and diameter D) of each tablet were measured using a Caliper (CD-15CPXR, Mitutoyo Deutschland, Neuss, Germany). The tablets tensile strength (σ_T) was calculated according to the following equation [17]:

$$\sigma_T = \frac{2\,F}{\pi\,D\,h} \quad \text{(Equation 2)}$$

2.3.3. Disintegration Time

The disintegrating time of 6 tablets was determined using a disintegration tester (PTZ Auto, Pharma Test Apparatebau, Hainburg, Germany) according to the Ph. Eur. [18] (section 2.9.1).

2.3.4. Friability

The friability of the tablets was determined using a friability tester (TAR, Erweka, Heusenstamm, Germany) according to the Ph. Eur. [18] (section 2.9.7).

2.4. ODT Characterization

2.4.1. Scanning Electron Microscopy (SEM)

The surface morphology of the tablets was evaluated using a Phenom® G2 PRO Desktop scanning electron microscope (Phenom-World, Eindhoven, Netherlands). Photos were taken at 20 and 430 x magnification using a voltage of 5 kV.

2.4.2. Wetting Time and Water Absorption

The wetting time of the tablets was evaluated using the simulated wetting test reported by Park, et al. [19]. A piece of folded filter paper was placed in a Petri dish of 3.6 cm in diameter and 2.0 cm height. The tablet was placed on the filter. 1.75 mL of an aqueous solution containing 1% (w/V) of brilliant blue 85 E 133 (Sicovit®, BASF, Ludwigshafen, Germany) was added at the bottom of the Petri dish. The total wetting time was measured and defined as the time required for the blue solution to diffuse through the tablet and completely cover its surface. The assay was performed using 10 tablets, individually. The tablets were weighted before and after the procedure to determine the rate of water absorption.

2.4.3. Dynamic Water Sorption

The water sorption and desorption of samples was measured at 25 °C in a dynamic water sorption system (SPS11, Projekt Masstechnik, Ulm, Germany). One cycle with a step variation of 10% relative humidity (RH) was performed, from 0 to 90% and 90 to 0% RH. The samples were measured in triplicate.

2.4.4. Uniformity of Content

The uniformity of content of the ODTs was evaluated by HPLC using the acceptance criteria in the section 2.9.6 of the Ph. Eur. [18] for 10 tablets. Liquid chromatography was carried out in a Hitachi HPLC (LaChrom Elite®, Hitachi, San Jose, USA). The used parameters were: isocratic mobile phase of methanol-phosphate buffer (0.01 mol·L^{-1}, pH 4.0) in a ratio of 80:20 (V/V); flow rate of 1 mL·min^{-1}; Hypersil® ODS column (250 x 4.6 mm, 5 µm particle size); and injection volume of 20 µL. The detection was performed by UV spectrophotometry at a wavelength of 232 nm (LaChrom Elite® UV-Vis detector L-2400, Hitachi, San Jose, USA). A calibration was previously performed using metformin HCl (EDQM primary standard reference) at concentration range of 0.01 to 0.06 mg·mL^{-1}. The calibration was performed in triplicate.

2.4.5. Drug Release Profile

The *in vitro* drug release profile was determined using paddle method for the tablets and basket method for the pellets according to Ph. Eur. [18] (section 2.9.3) employing dissolution apparatus AT6 (Sotax, Aesch, Switzerland). 900 mL purified water at 37 ± 0.5 °C was used as dissolution medium. The rotation speed of the paddles was set to 100 rpm. Samples were automatically collected each 10 min and were analyzed using an UV spectrophotometer (Lambda 40, Perkin Elmer, Rodgau, Germany) coupled to a continuous flow cuvette of 1.0 mm at a wavelength of 232 nm. Previously, a calibration curve (n = 3) was performed using metformin HCl solutions with concentrations from 0.025 to 0.15 mg·mL^{-1}.

2.4.6. Taste-masking Investigations

2.4.6.1. Drug Release Investigation Using In-line UV/VIS Probe

For in-line measurements of the first 2 min of dissolution, an UV transmission probe (T300-RT-UV-VIS, Ocean Optics, Ostfildern, Germany) connected via an optical fiber with a deuterium light source (Mikropak® DH-2000-BAL, Ocean Optics, Ostfildern, Germany) was used (λ = 232 nm). Pellet samples corresponding to

10 mg of metformin HCl were placed into cylindrical sinkers (n = 6). Regarding the ODTs, 6 tablets were evaluated individually. The assay was performed in 900 mL of demineralized water containing 0.001% (w/w) polysorbate 20 at 37 ± 0.5 °C employing a paddle stirrer (stirring speed: 100 rpm). Measurements were made each second and recorded using SpectraSuite v.2.0 Software (Ocean Optics, Ostfildern, Germany). A previous calibration procedure was performed using solutions of metformin HCl at a concentration range of 0.001 to 0.015 $mg \cdot mL^{-1}$.

2.4.6.2. Electronic Tongue Investigation

All measurements were performed using a taste sensing system TS-5000Z (Insent Inc., Atsugi-Chi, Japan). The electronic tongue was equipped with seven lipid membrane sensors, which are dedicated to different taste qualities (Table 3). The equipment parameters, such as washing steps and data collect times, were defined according to the work of Woertz, et al. [20]. For the equipment calibration, metformin HCl solutions of 0.01, 0.1, 0.5, 1.0, 2.5, 5.0, 8.5, 10.0, and 15.0 $mg \cdot mL^{-1}$ were previously evaluated. Individual samples of 10 tablets were stirred (100 rpm) in 100 mL demineralized water at 37 °C. After 30 and 60 s, the samples were immediately filtered through a 20 µm paper filter using a vacuum pump and direct measured by the electronic tongue. Data processing and graphical illustration of the results were carried out using Excel (Microsoft, Redmond, USA) and SIMCA® v.13.0.3 (Umetrics AB, Umea, Sweden).

3. Results and Discussion

3.1. Design of Experiments (DoE)

To investigate the effects of the compression force and amount of co-processed excipients on properties of tablet based on solid lipid pellets, tablets were produced and characterized regarding their tensile strength, disintegration time, and friability. These properties could be considered as the most important tablet quality attributes [9]. The results of the DoE investigations using Ludiflash® and Parteck® ODT are shown in Table 4. Unfortunately, tablet lamination phenomenon was observed for the batches produced at compression forces of 5.0 and 7.5 kN for the formulations containing 40 and 50% (w/w) of Parteck® ODT. As the data of the characterization of these tablets were not complete, a statistical model could not be constructed. Consequently, the model based on the experiments with Ludiflash® was than evaluated individually.

The data were evaluated by regression analysis (least squares fit), which provides a model relating changes/effects in the investigated factors (compression force and excipient fraction in the formulation) to the changes in the studied tablet properties (friability, disintegration time, and tensile strength of the tablets). Logarithmic transformation of the values of disintegration time and friability showed to improve the model quality. The quality of the obtained model for the investigated properties is presented in Table 5. According to Eriksson, et al. [21], goodness of fitness (R^2) alone is not sufficient for probing the validity of a model and a much better indication of the usefulness of the model is given by the goodness of prediction (Q^2). Regarding the observed values, the results of these both indicators reflect on the model validity value, which

shows that the models fit appropriately. Generally, values higher than 0.25 suggest a valid model. Furthermore, the indicators suggest a good quality for fitting and prediction of their effects on the investigated tablets properties, since their R^2 and Q^2 are higher than 0.5 and do not diverge more than 0.2 – 0.3 from each other [21].

The importance of the compression force and Ludiflash® fraction in the formulation was evaluated in terms of regression coefficients and contour plot of the factor´s effect on disintegration time, tensile strength, and friability. Fig. 1A displays the coefficient plot and its related contour plot regarding the disintegration time of the tablets (logarithmically transformed). ODTs were successfully obtained since some formulations showed disintegration times below 3 min, which is the disintegration time specified for ODTs by the Ph. Eur. [18]. Both investigated factors showed significant impact on the disintegration time of the tablets. An increase in Ludiflash® fraction reduces the disintegration time, while high compression forces increases it, as can be seen by their linear coefficients in the coefficient plot (Exc and Com, respectively). As Ludiflash® is based on 90% (w/w) of D-mannitol (a fast dissolving filler), high fractions in the tablet leads to a higher extent of contact with the surrounding water, resulting in a pronounced wetting and faster disintegration process. On the other hand, at lower Ludiflash® fractions, the proximity between the lipid pellets is decreased and solid lipid bridges could be form during the compression step, delaying the disintegration of the tablet. At maximum pressure point (when the upper and lower punches are at the nearest position from each other), heat is generated by inter-particular friction [22]. These conditions could lead to a partial melting of the lipids, which could stablish solid bridges (after solidification of the lipids) when the pression is cessed. However, further studies are still required to confirm this hypothesis.

No interaction effect between the both investigated factors was observed since the two-factor interaction coefficient (Exc*Com) is not statistically significant and, therefore, this coefficient was removed from the model to improve its quality. Quadratic effects for both factors were observed (Com*Com and Exc*Exc). Regarding the contour plot (Fig. 1A, right side), two distinguish effect regions can be highlighted: one at a low level of the Ludiflash® fraction (below 38%; w/w) and a second at its high level. At low levels of the excipient, the compaction force presents a negative influence on the disintegration time of the tablet: the higher the compression force, the longer is the disintegration time of the tablet. Besides, even at compaction forces around 2.5 kN, the disintegration time was not decreased below 3 min, time required to characterize the tablet as an ODT [18]. At this region, higher compression forces lead to a higher proximity between the lipid pellets, probably generating surface interactions or even producing solid bridges between them [23, 24] further affecting the disintegration process. On the other hand, at fractions of Ludiflash® (which increases physical separation of the pellets) above 34% (w/w) at low levels of compression force, or above 38% (w/w) at median to high levels of compression force, the disintegration time is highly decreased. However, at this region, the disintegration time does not suffer sufficient influence of the both factors to achieve times below 2-3 min.

The mechanical strength of a tablet is usually represented by its tensile strength and it is associated with the resistance of the tablet to fracture and/or attrition [9]. The effect of the investigated parameters on the tablet tensile strength is depicted in Fig. 1B. The resulted linear coefficients (Fig. 1B, left side) depict a stronger influence of compression force on the tensile strength compared to the fraction of co-processed excipient. A quadratic effect of the amount of Ludiflash® and an interaction effect between the both investigated factors are also observed. The overall results could be related to the increase of the proximity by primary particles and material deformation in the tablet due to the increase of the compression force. The effect of these alterations could lead to an increase in molecular and particular surface interactions among the components, increasing their cohesion and, consequently, the tablet resistance to fracture [24]. The second-most influential factor is the fraction of Ludiflash®, however, this factor generates a negative response. An increase in the fraction of co-processed excipient, from its standard concentration (40%; w/w) to its high fraction (50%; w/w) - while compression force is maintained at its standard condition (5.0 kN) - leads to a decrease of around 0.20 MPa in the tensile strength. Moreover, the two-factor interaction coefficient (Exc*Com) shows a negative and significant relation between compression force and fraction of Ludiflash® regarding the tensile strength of the tablet. This means that the effect of the compression force on the tensile strength depends on the fraction of Ludiflash® in the formulation. Likewise, the effect of the fraction of Ludiflash® on this tablet property is also dependent of the compression force. This overall effect can be seen in the contour plot (Fig 1B, right), which presents a relatively similar relationship between the factors effects on the tablet tensile strength. Given these points, relatively high tensile strength values (> 0.3 MPa) are observed in the region of high compression forces and Ludiflash® fractions below 42% (w/w). These results, regarding the effect of the compression force on the tensile strength of tablets based on mannitol as major excipient, are in accordance with the literature [25].

It is important to mention that there is no specified limit or values for tensile strength or resistance to fracture of tablets in the Ph. Eur. [18]. Herewith, considering further processes such as blistering, transportation, and posterior handling by the patient, the higher the tensile strength, the better the tablet mechanical strength to withstand fracture and erosion and, therefore, its quality regarding physical integrity [9]. It might be interesting to point that the overall observed values for tensile strength are quite low. Moreover, a high tensile strength value should be only considered as adequate if this attribute does not influence other tablet properties, in special the drug release profile.

Regarding the friability of the tablets, two of the formulations showed 100% (w/w) of friability, which means that they completely disintegrate during the assay (Table 4). Notably, these formulations present systems which are so different comparing to the other investigated formulations, that they negatively influence the interpretation of the used model. Considering that these formulations should not be used in the same model, the friability model will not be discussed in the present work. Regarding the observed values for friability presented in Table 4, high friability for the obtained tablets were observed for some formulations, which could be related to the low compression force range investigated in the present study (2.5-7.5 kN). High material loss (> 20%; w/w) was observed at high fractions of Ludiflash® and compression forces below

3.5 kN. The high presence of mannitol in Ludiflash® formulation could partially explain these observations, since this substance does not present sufficient binder properties against breakage compared to tablets based on less excipient.

Regarding the acceptance value of 1% (w/w) of maximal material loss for tablets defined in the Ph. Eur. [18], and considering the results observed in Table 4, all the tablets produced at 7.5 kN of compression force showed weight loss below this limit, denoting that this applied force is required to achieved adequate quality of ODTs. Considering the overall results (friability, disintegration time, and tensile strength), to obtain adequate ODTs, high compression force and high amount of Ludiflash® should be used. However, it is important to point that the investigated parameter values could be considered extreme high/high regarding their position in the design space. Although adequate characteristics of the tablets were successfully achieved (considering the values defined by the Eur. Ph. for ODTs), these results could present a certain limitation of the DoE study and an optimization step should be performed to further investigate the influence of these parameters at even higher levels.

3.2. ODTs with Ludiflash®

Based on the results of the DoE, a batch of 1,000 tablets were produced containing 50% (w/w) of Ludiflash®, as ready-to-use excipient, and using a compression force of 7.5 kN to obtain ODTs with adequate characteristics. These ODTs were then further characterized.

3.2.1. Morphological Characterization

Ideally, pellets to be contained in a multiple-unit system as tablets should not fuse into a non-disintegrating matrix during the compaction step to avoid alterations on their properties, such as drug release profile and disintegration of the obtained tablet [7, 26]. This is especially problematic for tablets containing APIs that should be fast released, such as metformin HCl. Therefore, to develop ODTs containing solid lipid pellets maintaining immediate drug release profile of the multiparticulates, the use of additional excipients should be considered. These excipients should present two main functions: (1) avoid the formation of a insoluble monolithic lipid matrix and (2) improve the disintegration properties of the ODTs.

To investigate if the presence of Ludiflash® provides adequate physical protection and separation of the pellets after the compression step, photos of the surface of the obtained tablets were taken. Optical images of the ODT surface and SEM photos of one single lipid pellet at the tablet surface are depicted in Fig. 2. It is possible to recognize the pellets dispersed at the tablet surface and surrounded by the excipient (Fig. 2A). A closer look into the tablet surface shows that the lipid pellet structure remains intact after compression (Fig. 2B and Fig. 2C). Due to the viscoelastic deformation behavior of the solid lipids [27, 28] contained in the pellet formulation, they were not crushed but slightly deformed. Furthermore, typical plastic deformable materials, which are also contained in the pellet, promote partial volume reduction of the pellet by local surface deformation involving flattening of pellets [29]. This deformation phenomenon can be recognized in the SEM photos.

The pellets may deform but should not rupture. The presence of cracks at the pellet surface may have undesirable effects on the drug release properties of the subunits [7]. As can be seen, the maintenance of the pellets main structure could indicate that properties of this subunit, such as taste-masking and drug release profile, should not be influenced by the compression process in the investigated range of compression force. Besides, no cracks at the pellet surface were evidenced.

The friability (0.41%; w/w), tensile strength (0.53 ± 0.06 MPa), and disintegration time (1.27 ± 0.13 min) values for this batch of ODTs are like those observed in the same ODT formulation during the DoE (50% of Ludiflash®; w/w). In addition, tablet friability below 1% (w/w) and disintegration time below 3 min were observed and are in accordance with the specified limits in the Ph. Eur. [18].

3.2.2. Water Absorption, Sorption, and Wetting Test

The visual start and endpoint of the simulated wetting test of the ODTs are shown in Fig. 3. It is possible to observe that the water absorption starts from the surroundings of the tablet (Fig. 3B) until a complete wetting is achieved (Fig. 3D). The complete water absorption process took about 3.02 ± 0.90 min. Furthermore, an increase in the tablet mass of 43.4 ± 1.9% (w/w) was observed, after 6 min. Longer exposure to water did not increase the water uptake by the ODTs.

As lipids are mainly hydrophobic and are present in the ODT formulation at a fraction of around 15% (w/w), they do not seem to significantly influence the wettability and water uptake by the tablets. Therefore, the water absorption is mainly result of the presence of mannitol (a fast-dissolving filler) and metformin HCl, which is freely soluble in water [18, 30, 31]. These substances represent around 80% (w/w) of the total of the ODT formulation. It is important to point, that the initial water content of the ODTs showed a value of 0.73 ± 0.02% (w/w).

The water sorption and desorption isotherms exhibit by the ODTs and the lipid pellets are depicted in Fig. 4. The pellets separately (LP_{70}) showed a weight increase of 1.73 ± 0.02% (w/w) after exposure to a RH of 90%. This water sorption could be pointed as mainly caused by the metformin HCl, which exhibits hygroscopic characteristics [32]. On the other hand, the ODTs (which are based on 50% (w/w) of LP_{70}) showed a weight increase of 3.61 ± 0.04% (w/w). This value is relatively low compared to the results of water uptake in the simulated wetting test. Comparatively, this difference is probably promoted by the presence of mannitol and crospovidone in the ODT formulations.

Although the lipid pellets exhibit a higher superficial area compared to one single tablet, it is important to highlight that the ODTs showed a porosity around 19% (w/w), which plays a key role in the water adsorption mechanism. The water adsorption isotherms of the ODTs show a slight increase in their masses until a RH of 80% (Fig. 4). Above this point, a higher water adsorption is observed until equilibrium is achieved. Interestingly, a similar pattern is also exhibited by the pellets, indicating that metformin HCl plays a key role on the water adsorption by the formulation. In contrast, the water desorption of the ODTs showed a small hysteresis, probably due to the tablet dimensions and presence of the porous system, since the water vapor

requires more time (due to a longer path compared to the pellets) to escape the inner core of the ODT. Still, after decreasing the relative humidity, the complete water vapor is removed, indicating that superficial adsorption is the main water adsorption mechanism [33].

3.2.3. Drug Release Profile

According to Klancke [34], taste-masked ODTs should be formulated in such a manner, that a small delay in drug release is present and it should be long enough to pass through the oral cavity, been followed by a fast and complete release of the API. The obtained ODTs showed an API content of 99.54 ± 4.72% (w/w), what is in accordance with specifications of both monographs referred to the label claim in the Ph. Eur. [18]: uniformity of content (section 2.9.6) and uniformity of dosage units (section 2.9.40). The drug release profile of the ODTs is depicted in Fig. 5A. A short lag time can be observed within the first 2 min of dissolution, followed by a release of 85% (w/w) of metformin HCl, after around 28 min and 100% (w/w) being release after 40 min. These results characterize them as immediate-release tablets according to the USP 34 [35].

Besides, the drug release profile of multiparticulates in a multiple-units system, like a tablet containing pellets, should not be strongly affected by the compaction process [7]. A comparison of the drug release profiles between the ODTs and lipid pellets (LP_{70}) is depicted in Fig. 5A. It is possible to point that the compression step did not present strong influence on the drug release profile of the pellets, since similar profiles are observed. However, the initial lag time observed for the ODTs within the first minutes of dissolution is not present in the LP_{70} profile. Given that, this lag time is probably related to the water uptake and disintegration process of the tablet. However, this lag time does not present strong influence on the drug release kinetic of the ODT, since 100% (w/w) of metformin HCl is released after around 45 min, similarly to the original pellets. Thus, regarding taste-masking approach, this slight alteration in the drug release should be considered, since the lag time could positively influence the taste-masked properties of the tablet [5].

3.2.4. Taste-masking Investigations

3.2.4.1. In-line Drug Release Assay (UV/Vis Probe)

An in-line drug release assay was performed to investigate the extension of the lag time generated by the compression process and to correlate it to further investigations by electronic tongue. The results of the drug release within the first 2 min of dissolution are depicted in Fig. 5B. The ODTs released 0.20% (w/w) of metformin HCl after 30 s and approximately 0.90% (w/w) after 60 s. These both sampling times (30 and 60 s) were defined based on works that described these sampling times as more representative for taste-masking investigations [6, 36]. After 2 min, only 2.4% (w/w) of metformin HCl was released while the LP_{70} released around 25% (w/w) of the API. Regarding these relatively small values, it could be inferred that the ODTs present taste-masked properties. Unfortunately, after this time, using the described equipment, the concentration of metformin HCl in the medium was outside the Lambert-Beer linear range and was not possible to further investigate to direct correlate the results with the on-line assay (until 60 min).

The FIP/AAPS guideline suggests that a solid oral dosage form can be considered as taste-masked if a drug release of less than 10% (w/V) is achieved until 5 min of dissolution [37]. The previous results regarding the drug release profile show that around 12% (w/V) of metformin HCl is released until 5 min of the assay (Fig. 5A), which do not characterize the ODT as taste-masked according this guideline. However, this value of 10% (w/V) is not applicable to individually judge about taste-masking effects since it is highly dependent on the human perception threshold for each individual substance and on the dissolution method used [36]. Likewise, 5 min could be considered an unrealistic time for oral solid dosage forms, especially regarding tablets or ODTs, considering that their length of stay in the oral cavity should be relatively short (few seconds to around 2 min) [38]. Therefore, other additional methods need to be employed to further investigate taste-masked properties and correlate it to these dissolution results [6]. In the present work, an electronic tongue investigation was performed to provide complementary information and to correlate it to the dissolution results. Additionally, an investigation time of 1-2 min will be considered, during the present work, as more representative for further discussions about taste-masking properties of the ODTs.

3.2.4.2. Electronic Tongue Investigation

The taste-masked properties of the ODTs were investigated by electronic tongue method comparing them to pure metformin HCl (unpleasant taste reference) and to a drug-free tablet (pleasant-taste reference – "placebo") produced by direct compression. The tablet was based on a mixture of Ludiflash®, hard fat, glyceryl distearate, and trimyristin in the ratio of 10:4:1:1 (w/w), respectively. Samples for the equipment were prepared based on times of 30 and 60 s, since these values represent a more realistic residence time of a orodispersible tablet in the oral cavity before swallowing [36, 38]. The principal component analysis (PCA) from the MVDA results of the sensor set resulted in a bi-dimensional map, depicted in Fig. 6A, where 84.6% of the data information is contained in the first principal component (PC1) and 13.4% in the second principal component (PC2). The correspondent loading plot is presented in Fig. 6B. Considering only the PC1 results, a strong impact of the sensor responses for bitter taste (SB2AN0, SB2AC0, and SB2C00) were observed for pure metformin HCl. This result corroborates reports in the literature regarding the strong bitter taste presented by this API [15, 36, 39]. In contrast, the drug-free formulation generated higher responses on the sensors related to astringency (SB2AE1) and saltiness (SB2CT0).

Regarding the PCA map (Fig. 6A), a clear proximity of the ODTs samples to the pleasant-taste reference is observed in comparison to the unpleasant taste reference. Among all samples, the ODT sample of 30 s (ODT_30s) showed the most prominent taste-masked properties, since it is the closest to the pleasant-taste reference. Moreover, considering the correlation between concentration and taste perception, the longer the sampling time, the higher the drug release, the higher the sensor response to the bitter taste of metformin HCl. Besides, these results are in accordance with the UV probe assay since the drug release investigations of the ODTs showed a slighter release metformin HCl at 30 s (0.20%; w/w) compared to 60 s (0.90%; w/w). However, the ODT sample after 60 s can also be assumed as presenting taste-masked properties when compared to the unpleasant reference. Moreover, comparing these times to the disintegration time presented

by the tablets (1.27 ± 0.13 min), it is possible to assume that during this process period, the release of the drug and the taste perception should be relatively low.

Likewise, the tablet sample of 30 s (ODT_30s) showed significant improvement in its taste-masked properties compared to the pellet sample at the same sampling time (LP70_30s). Interestingly, at longer times, the ODTs are near positioned to the LP_{70} (30 s), in the central region of the PCA map, indicating a relative similar taste response between these two samples after 60 s. Considering the distances of the samples in the PCA map, these observations do not completely corroborate the previous observed drug release results, which showed a relatively lower drug release from the ODTs within 30 and 60 s (0.20 and 0.90%, respectively) compared to the LP_{70} at same times (13.2 and 18.8%, respectively). Even though, the taste-masked properties of the ODTs were confirmed regarding the proximity of the samples to the pleasant reference formulation and do to their low drug release within the first minutes of dissolution.

4. Conclusions

A DoE was performed to investigate the influence of compression force and amount of two mannitol based co-processed excipients (Ludiflash® and Parteck® ODT) on properties of ODTs based on solid lipid pellets containing metformin HCL. During the compression step investigations, a strong lamination of the tablets containing Parteck® ODT was observed and these tablets were not further evaluated. Compression force and amount of Ludiflash® presented strong influence on the disintegration time of the tablets. However, disintegration times below 3 min were achieved, characterizing the tablets as ODTs according to the definition of the Ph. Eur. [18]. Likewise, tablets presenting adequate friability and tensile strength were successfully obtained at higher compression forces and high amounts of the excipient. The compression step did not generate breakage or ruptures of the lipid pellets, resulting only in a slight superficial deformation of them. As result, the obtained ODTs presented similar drug release properties to the original lipid pellets. A lag time in the first minutes of dissolution of metformin HCl from the ODTs was observed, which was mainly a result of the compression process. However, the presence of this lag time did not influence the drug release profile and tablets presenting immediate-drug release kinetic were obtained. A principal component analysis (PCA) of the results of an electronic tongue assay showed a significant improvement in the taste-masked properties of the ODTs compared to an unpleasant-taste reference. The overall results indicate the maintenance of taste-masking properties of the lipid pellets after compression and even a slight improvement of this property without interfering in the drug release kinetic of the original lipid pellets.

Conflict of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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Table captions

Table 1. Factors investigated in the DoE

Table 2. ODT formulations

Table 3. Sensors for the taste sensing system and corresponding taste sensations

Table 4. DoE data

Table 5. Quality of the experimental design using Ludiflash® as ready-to-use excipient

Figure Captions

Figure 1. Regression coefficients (left) and response contour plot (right) regarding (A) tablet disintegration time and (B) tablet tensile strength (ODTs with Ludiflash®). Data was centered and scaled.

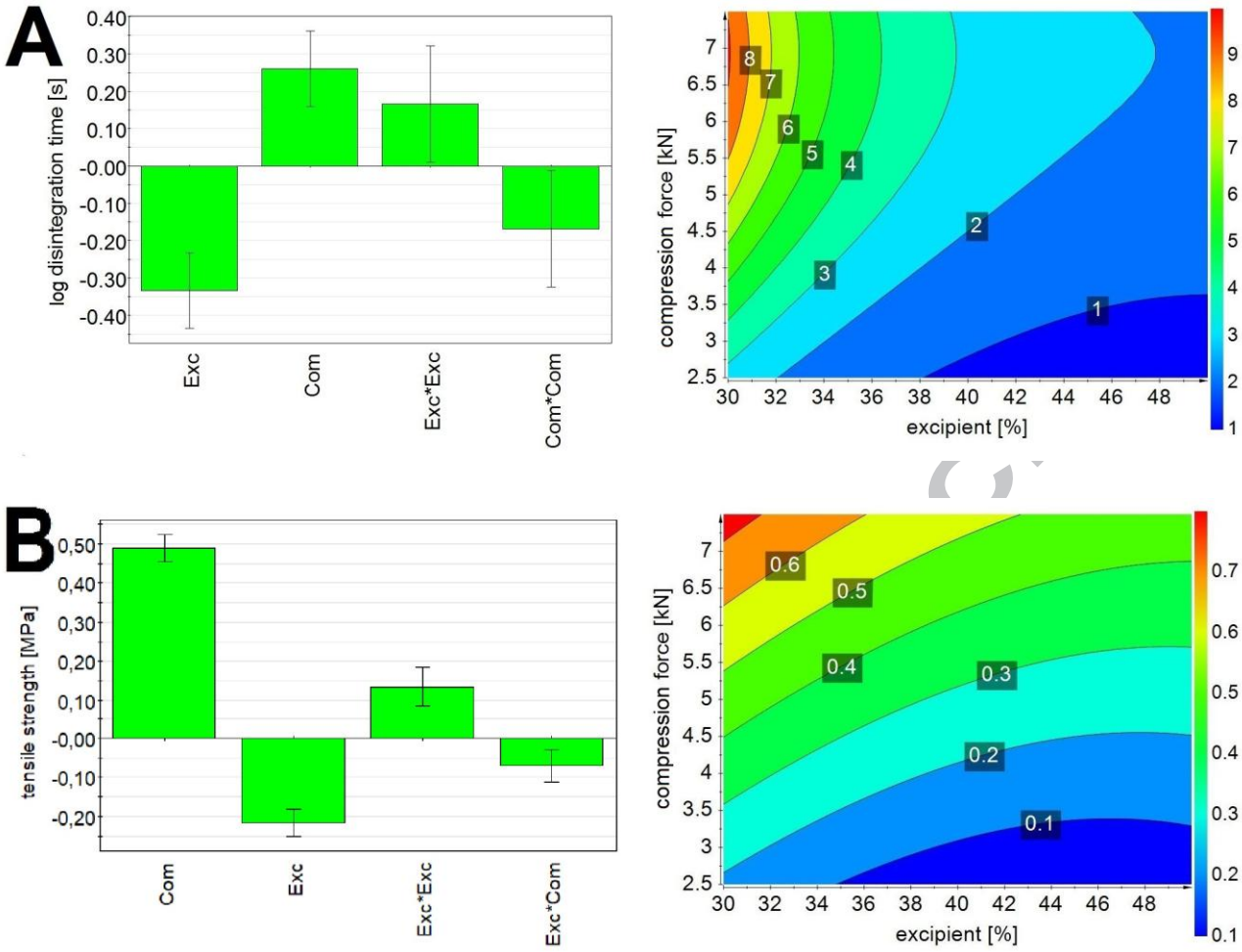
Figure 2. SEM photos of the ODT surface taken at (A) 20x magnification, (B) 430x magnification, and (C) tablet sectional cut at 20x magnification (scale represents 6 mm, 310 µm, and 6 mm, respectively).

Figure 3. Simulated wetting test visual observations: (A) starting and (D) end point.

Figure 4. Water sorption and desorption curves of ODTs in comparison with the lipid pellets LP_{70} (n = 3; mean ± SD).

Figure 5. Metformin HCl release from ODT and from LP_{70}: (A) on-line drug release by dissolution test apparatus using basket method for pellets and using paddle method for ODTs (100 rpm) (mean ± SD, n = 6). (B) In-line drug release by UV/Vis probe, paddle method at 100 rpm (mean ± SD, n = 3). Dissolution media: 900 mL purified water containing 0.001% (w/w) polysorbate 20, temperature of 37 °C ± 0.5, λ = 232 nm.

Figure 6. (A) PCA map obtained by multivariate data analysis of metformin HCl and (B) its correlated loading plot: ODTs compared to LP_{70} performed by electronic tongue (data was mean centered).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0.20
0.10
-0.00
-0.10
-0.20
-0.30
-0.40
Exc
Com
Exc*Exc
Com*Com
compression force [kN]
excipient [%]
8
7
6
5
4
3
2
1
B
tensile strength [MPa]
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0,40
0,30
0,20
0,10
-0,00
-0,10
-0,20
Com
Exc
Exc*Exc
Exc*Com
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excipient [%]
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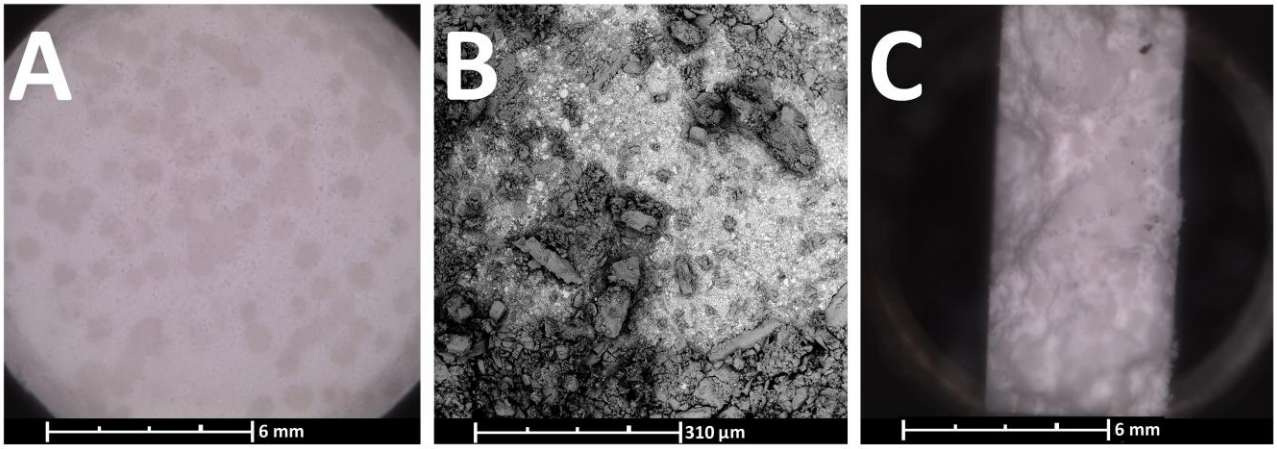
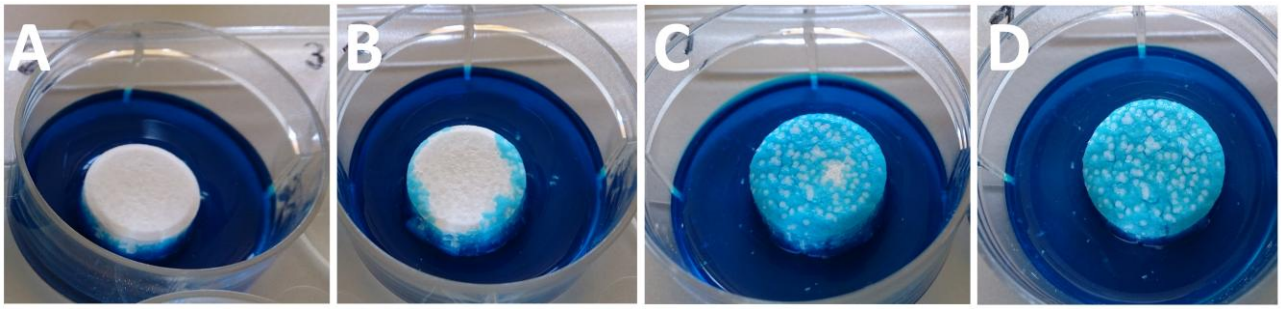
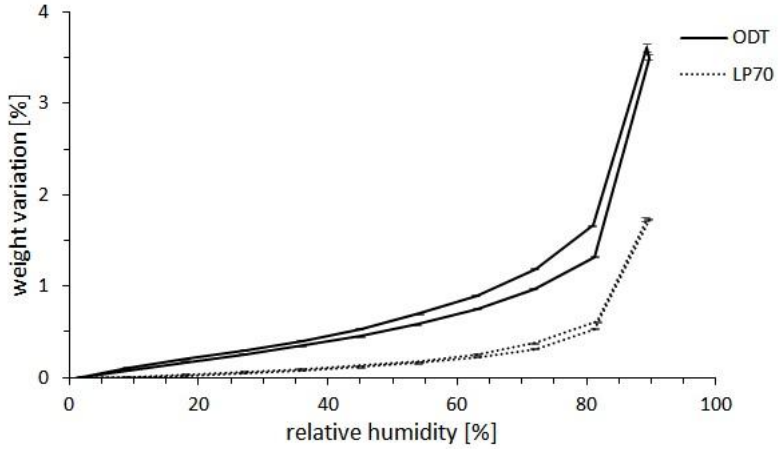
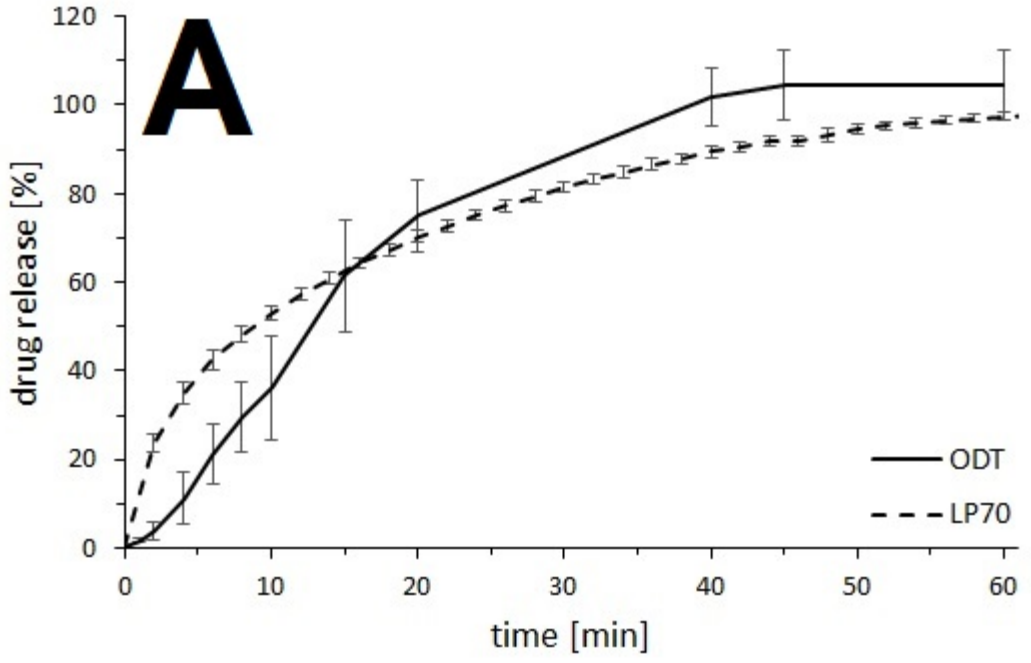
0.4
0.3
0.2
0.1





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50
60

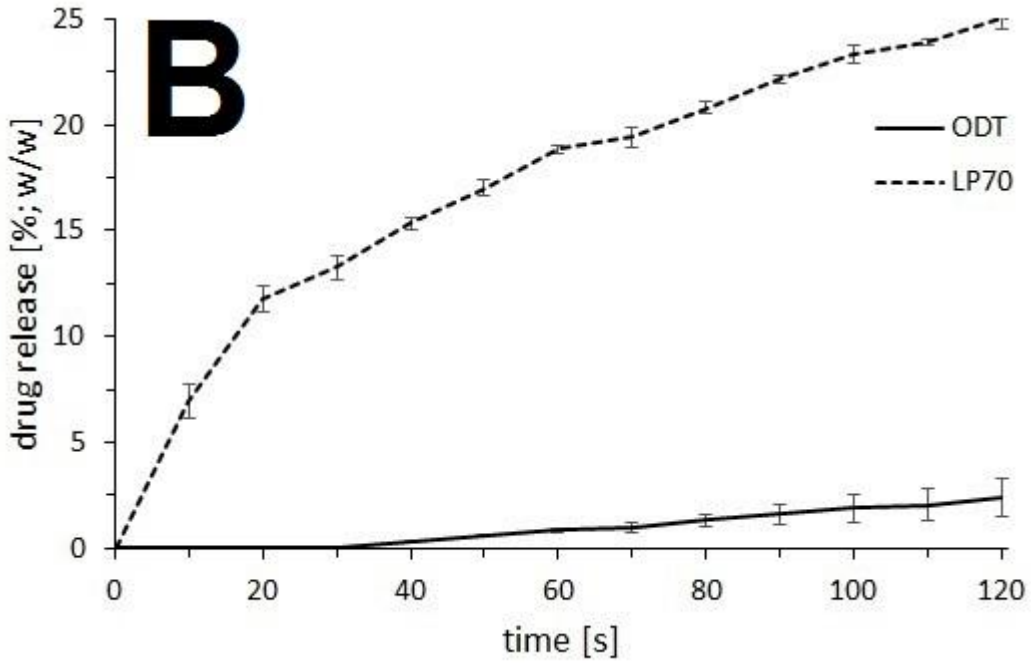
B
drug release [%; w/w]
time [s]
ODT
LP70
0
5
10
15
20
25
0
20
40
60
80
100
120

Table 1. Factors of the DoE

Factors	Factor level		
	-1	0	+1
Compression force (Com) (kN)	2.5	5.0	7.5
Co-processed excipient (Exc) (%; w/w)	30	40	50

Table 2. ODT formulations

Component (%)	1	2	3	4	5	6
Metformin HCL lipid pellets	70*	60*	50*	70*	60*	50*
Ludiflash®	30	40	50	-	-	-
Parteck® ODT	-	-	-	30	40	50
Final tablet weight (g)	1.142	1.285	1.428	1.142	1.285	1.428

*Corresponding to 500 mg of metformin HCl

Table 3. Sensors for the taste sensing system and corresponding taste sensations

Sensor type	Sensor name	Corresponding taste sensation
SB2AAE	umami sensor	umami
SB2CT0	saltiness sensor	saltiness
SB2CA0	sourness sensor	sourness
SB2AE1	astringency sensor	astringency
SB2AC0	bitterness sensor 1	bitterness of cationic substances
SB2AN0	bitterness sensor 2	bitterness of cationic and neutral substances
SB2C00	bitterness sensor 3	bitterness of anionic substances
Reference electrode		

Table 4. DoE of ODTs: factors and responses

	Ludiflash®					
	Factors		Responses			
			Mean ± SD (n = 10)			
	Excipient content (%)	Compression force (kN)	Tensile strength (MPa)	Crushing force (N)	Disintegration time (min)**	Friability (%)
N1	30	2.5	0.182 ± 0.046	24.0 ± 6.1	3.22 ± 0.97	12.95
N2	30	5.0	0.452 ± 0.111	57.1 ± 14.2	7.68 ± 4.21	0.38
N3	30	7.5	0.748 ± 0.044	91.4 ± 5.8	7.05 ± 3.60	0.26
N4	40	2.5	0.041 ± 0.014	7.0 ± 2.3	0.68 ± 0.14	100.00
N5*	40	5.0	0.310 ± 0.126	47.4 ± 19.0	2.12 ± 1.02	2.17
N6	40	7.5	0.518 ± 0.061	72.9 ± 8.5	3.88 ± 1.96	0.31
N19*	40	5.0	0.269 ± 0.090	38.9 ± 12.8	2.74 ± 1.36	4.19
N20*	40	5.0	0.289 ± 0.141	42.8 ± 19.4	1.89 ± 0.43	1.67
N7	50	2.5	0.041 ± 0.014	8.3 ± 2.9	0.61 ± 0.14	100.00
N8	50	5.0	0.226 ± 0.031	41.8 ± 5.7	1.60 ± 0.83	3.39
N9	50	7.5	0.466 ± 0.080	79.5 ± 12.7	1.78 ± 0.36	0.89
	Parteck® ODT					
	Factors		Responses			
			Mean ± SD (n = 10)			
	Excipient content (%)	Compression force (kN)	Tensile strength (MPa)	Crushing force (N)	Disintegration time (min)**	Friability (%)
N10	30	2.5	0.184 ± 0.028	23.5 ± 3.5	1.12 ± 0.44	11.7
N11	30	5.0	0.398 ± 0.078	49.9 ± 9.7	5.76 ± 1.90	0.45
N12	30	7.5	0.586 ± 0.192	71.7 ± 22.9	6.36 ± 1.29	0.34
N13	40	2.5	0.039 ± 0.029	10.0 ± 1.7	0.60 ± 0.23	100.0
N14*	40	5.0	0.238 ± 0.114	36.2 ± 16.6	1.96 ± 1.79	5.82
N15	40	7.5	***	***	***	***
N21*	40	5.0	0.194 ± 0.089	28.9 ± 13.0	1.6 ± 0.60	***
N22*	40	5.0	0.185 ± 0.044	27.7 ± 6.1	2.09 ± 1.19	6.18
N16	50	2.5	0.059 ± 0.021	11.2 ± 4.0	1.18 ± 1.02	7.49
N17	50	5.0	0.138 ± 0.024	25.0 ± 4.3	1.13 ± 0.56	23.08
N18	50	7.5	***	***	***	***

* Center points; ** n = 6; *** Not measured due to tablet lamination.

Table 5. Quality of the experimental design using Ludiflash® as ready-to-use excipient

	Tensile strength	Disintegration time	Friability
Goodness of fit (R^2)	0.9962	0.9506	0.9680
R^2 adjusted	0.9929	0.9176	0.9360
Goodness of prediction (Q^2)	0.9853	0.8115	0.7631
Model validity	0.9273	0.7664	0.7925
Reproducibility	0.9906	0.9453	0.9491